

Open Access Publications

2018

Relationship between symptomatic and functional improvement and remission in a treatment response to stimulant trial

Margaret Weiss

University of Arkansas for Medical Sciences

Ann Childress

Center for Psychiatry and Behavioral Medicine, Inc.

Greg Mattingly

Washington University School of Medicine in St. Louis

Earl Nordbrock

Rhodes Pharmaceuticals L.P.

Robert J. Kupper

Rhodes Pharmaceuticals L.P.

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Weiss, Margaret; Childress, Ann; Mattingly, Greg; Nordbrock, Earl; Kupper, Robert J.; and Adjei, Akwete L., "Relationship between symptomatic and functional improvement and remission in a treatment response to stimulant trial." *Journal of Child and Adolescent Psychopharmacology*.28,8. 521-529. (2018).

https://digitalcommons.wustl.edu/open_access_pubs/7713

Authors

Margaret Weiss, Ann Childress, Greg Mattingly, Earl Nordbrock, Robert J. Kupper, and Akwete L. Adjei

Relationship Between Symptomatic and Functional Improvement and Remission in a Treatment Response to Stimulant Trial

Margaret Weiss, MD, PhD, FRCP(C)¹ Ann Childress, MD² Greg Mattingly, MD^{3,4}
Earl Nordbrock, PhD⁵ Robert J. Kupper, PhD⁵ and Akwete L. Adjei, PhD⁵

Abstract

Objective: To evaluate the relationship between symptom and functional improvement and remission in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) enrolled in an 11-week open-label dose-optimization phase of an methylphenidate extended release (MPH-MLR) pivotal study.

Methods: Assessments included the Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) and ADHD Rating Scale, Fourth Edition (ADHD-RS-IV). Definitions included the following: symptom improvement ($\geq 30\%$ decrease in ADHD-RS-IV total score); symptom remission (ADHD-RS-IV total score ≤ 18); functional improvement (decrease in WFIRS-P total score ≥ 0.25 [minimally important difference]); and functional remission (WFIRS-P total score ≤ 0.65).

Results: Two hundred children completed the open-label phase. At initial assessment, functional impairment was evident across all WFIRS-P domains and similar between children and adolescents. Those who were treatment naive had more functional impairment (WFIRS-P total: 0.82 vs. 0.70, $p=0.02$). Significant improvements in all WFIRS-P domains were noted at open-label end ($p<0.001$), with the largest improvement in Learning. At open-label end, 94% of children and adolescents demonstrated symptom improvement, of which 57% also showed functional improvement, and 75% of children and adolescents showed symptom remission, of which 81% also showed functional remission.

Conclusions: Children and adolescents treated with MPH-MLR showed moderate-to-large improvement in functioning during 3 months of treatment, both overall and in specific domains. However, a significant number of those who would be considered symptomatic responders failed to show improvement in functioning or continue to have significant functional impairment. Treatment with MPH-MLR showed that both symptomatic and functional remission are achievable goals. Identification of children and adolescents who have been successfully treated for their symptoms, but continue to suffer functional impairment, will allow us to offer additional targeted treatment interventions over and above medication to address residual difficulties.

Keywords: attention-deficit/hyperactivity disorder (ADHD), Weiss Functional Impairment Rating Scale-Parent (WFIRS-P), MPH-MLR, functional impairment

Introduction

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD), as defined by the *Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition* (DSM-5), includes behavioral symptoms

and functional impairments that extend across more than one setting (American Psychiatric Association 2013). Thus, ADHD is a multi-dimensional disorder requiring that evaluations of new therapies include a variety of assessments (Epstein and Weiss 2012). Although the symptoms of ADHD (inattention, hyperactivity, and impulsivity)

¹University of Arkansas for Medical Sciences, Child and Adolescent Psychiatry, Child Study Center, Little Rock, Arkansas.

²Center for Psychiatry and Behavioral Medicine, Inc., Las Vegas, Nevada.

³Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri.

⁴Midwest Research Group, St. Louis, Missouri.

⁵Rhodes Pharmaceuticals L.P., Coventry, Rhode Island.

Previous presentation: Parts of these data were presented at the American Academy of Child and Adolescent Psychiatry 63rd Annual Meeting, October 24–29, 2016, New York, NY; and the American Professional Society of ADHD and Related Disorders 2017 Annual Meeting, January 13–15, 2017, Washington, DC.

Funding: Funding for this analysis was provided by Rhodes Pharmaceuticals, L.P.

© Margaret Weiss et al. 2018; Published by Mary Ann Liebert, Inc. This Open Access article is distributed under the terms of the Creative Commons Attribution Noncommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and the source are cited.

are generally well recognized, it is often functional impairment that results in entry into the healthcare system for patients and their families (Epstein and Weiss 2012). Functional impairment encompasses the inability to complete tasks at school or at home, has a substantial impact on a child's or adolescent's ability to have meaningful friendships, and can have a negative impact on family relationships (Buitelaar and Medori 2010).

The primary endpoint in evaluations of new ADHD medications is usually symptom improvement or symptom remission to identify responder status. Although there have been various definitions of these categories, symptom improvement is usually defined as a 30% decrease in symptoms, or much improved (2) or very much improved (1) on the Clinical Global Impressions-Improvement (CGI-I) scale (Guy 1976). Symptom remission has been described as either a 40% or even 50% improvement in symptoms or a final mean symptom score of 1.0 (Swanson et al. 2001). It should be noted that these definitions have been shown to be highly correlated with one another (Mattingly et al. 2017).

Nonetheless several important caveats should be considered. The concept of "remission," borrowed originally from the depression literature as a predictor of relapse (Quitkin et al. 2005), is not consistent with the concept of ADHD as a neurodevelopmental disorder. In addition, the concept of improvement and remission was originally developed by Swanson et al. (2001) on somewhat arbitrary criteria with no reference to normative symptom scores in the population. For example, normative values for adolescent girls are much lower than for preschool boys, and using the same definition of remission for both may be inappropriate (Molina et al. 2009). We have adopted the consensually agreed upon term "remission" to indicate a robust improvement in symptoms or functioning, without necessarily implying that the patient is free of difficulty or at risk for return of symptoms given a change in treatment or circumstances (Molina et al. 2009).

There is also a conceptual difference between how much better symptoms are (i.e., percentage improvement) and how well the patient is at endpoint. To illustrate this difference, if a patient has a baseline score of 54 and shows full "response" status because he is 50% improved, his final score at endpoint is 27, which might still be clinically significant, especially if the residual symptoms were concentrated in either the inattentive or hyperactive/impulsive domains. Similarly, a patient with a baseline symptom score of 27, who has a 30% improvement, might end up in the normal range. This means that definitions of outcome need to look at percentage change as well as endpoint and improvement as well as remission, and be anchored outside of core symptoms in treatment targets relevant to the patient's presenting problem or functional impairment.

These definitions of symptom improvement and remission do not reference functional improvement or remission. Information regarding the existence of a treatment effect, statistical significance, or the magnitude of significance as measured by effect size has no bearing on clinical significance or impact on a patient's life. Clinical significance has been variously defined as a level of change that is recognizable by others, normative levels of functioning by the end of treatment, or failure to meet diagnostic criteria (Jacobson and Truax 1991). To determine clinical significance within a treatment model, it is also necessary to show both that the change reflects more than the fluctuations of the measure (Reliable Change Index) and the change indicates the patient is no longer dysfunctional, is in the normal range of functioning, or is functioning closer to the mean of the functional population than the mean of the dysfunctional population (Jacobson and Truax 1991). While these are very different definitions of clinical

significance, they are all based on establishing a functional outcome standard that goes beyond symptoms.

The focus of this study was to look at symptom improvement and remission by referencing these predefined outcomes against improvement and remission in functional impairment. There are no studies we are aware of that have empirically examined whether patients who are classified as "responders" are actually doing well as defined by a normative standard for functional well-being. While some research reflecting the impact of specific compounds on functional impairment has been conducted (Banaschewski et al. 2013), there remains a need to better understand how a pharmacotherapeutic intervention for ADHD might impact functional outcomes and the relationship between change in symptoms and change in functioning. Recent research has consistently demonstrated, particularly in pharmacological clinical trials, that the relationship between change in symptoms, functioning, and quality of life is modest, and that inclusion of multiple outcomes is necessary to provide the clinician with information needed to determine whether and what type of further intervention the patient needs.

Methods

Data for this *post hoc* analysis were taken from a randomized, double-blind, placebo-controlled, parallel, forced-dose study (ClinicalTrials.gov identifier NCT01239030) evaluating the safety and efficacy of four dose levels of methylphenidate extended release (MPH-MLR; 10, 15, 20, and 40 mg) compared with placebo in 230 children (67% male) and adolescents (6–18 years of age) with ADHD. The primary outcomes and complete study design have been published previously (Wigal et al. 2015). Briefly, this was a four-phase study that included the following: screening, 1-week forced-dose double blind, 11-week open label, and follow-up. The primary outcomes and complete study design have been published previously (Wigal et al. 2015). Since the 1-week double-blind period was shorter than the observation period and past study of sensitivity to change of the Weiss Functional Impairment Rating Scale (WFIRS), the data reported here are based on the open-label phase. Children and adolescents with all ADHD subtypes (except Not Otherwise Specified) were included in this study (Wigal et al. 2015). A baseline ADHD Rating Scale, Fourth Edition (ADHD-RS-IV) (DuPaul et al. 1998) total or subscale score \geq 90th percentile relative to the general population by age and sex was required at screening or baseline. In addition, an Estimate Full Scale intellectual level \geq 80 on the four-subtest form of the Wechsler Abbreviated Scale of Intelligence™ (Axelrod 2002) was required. Severe concomitant psychiatric disease or chronic medical illness were reasons for exclusion (Wigal et al. 2015).

MPH-MLR (Rhodes Pharmaceuticals L.P., Coventry, RI) (Aptenio XR® 2015) is an extended-release formulation of methylphenidate that was approved in 2015 by the U.S. Food and Drug Administration. MPH-MLR given once daily in capsule form or sprinkled on applesauce demonstrates a biphasic release that includes a first peak at \sim 2 hours following administration and a second attenuated peak at \sim 8 hours post administration, and sustained levels through at least hour 12 (Adjei et al. 2014). The two pivotal studies of MPH-MLR showed a positive benefit of treatment on symptoms of ADHD in children and adolescents (Wigal et al. 2014, 2015). Symptomatic response and remission with MPH-MLR have been described previously (Mattingly et al. 2017). Functional outcomes were assessed in the larger MPH-MLR pivotal study (Wigal et al. 2015) as a secondary outcome. We evaluated the functional characteristics of children and adolescents with ADHD enrolled in this study and compared the relationship

between clinical response or remission and functional outcomes after 11 weeks of open-label treatment with MPH-MLR.

The study protocol, amendments, and informed consent form were reviewed and approved by an institutional review board for each study site. The study was conducted in compliance with Good Clinical Practice guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, the United States Code of Federal Regulations that relates to clinical trial conduct, and the principles of the Declaration of Helsinki. All enrollees and/or their guardian provided informed consent before screening assessments.

Functional and symptom assessment

The WFIRS-Parent (WFIRS-P) and ADHD-RS-IV were assessed at baseline (beginning of double-blind phase), end of double blind, and end of open label.

WFIRS-P is a parent-rating scale that assesses functional impairment in the following domains: Family; Learning and School (including subdomains of Learning and Behavior); Life Skills; Child's Self-concept; Social Activities; and Risky Activities (Canadian ADHD Resource Alliance [CADDRA], 2011). WFIRS-P uses a 50-item scale, with each item rated on the following 4-point scale: 0 = never or not at all; 1 = sometimes or somewhat; 2 = often or much; and 3 = very often or very much or NA = not applicable (Canadian ADHD Resource Alliance 2000). The total score is the mean score for all items and the domain score is the mean score of the items in each domain. The WFIRS-P has shown strong psychometric properties in clinical settings (Tarakçıoğlu et al. 2015), research populations (Gajria et al. 2015), and population samples (Hadianfard et al. 2017). Internal consistency was demonstrated by alpha >0.9 for the measure as a whole and >0.7 for all domains (Gajria et al. 2015); test-retest reliability was evidenced by $r > 0.7$ after 1–4 weeks; moderate to strong correlations between each domain and the scale as a whole; and confirmatory factor analysis of the domains (Weiss et al. 2005, 2007; Molina et al. 2009; Qian et al. 2011; Gajria et al. 2015; Punyapas et al. 2015; Tarakçıoğlu et al. 2015; Dose et al. 2016; Hadianfard et al. 2017).

The minimal important difference (MID) of a clinically meaningful change over time for the WFIRS-P is a mean score of 0.25, as determined by use of three different methods (1/2 standard deviation [SD], standard error of the mean, and patient anchors of when they saw a significant change) (Hodgkins et al. 2016). This can be considered a reasonable and empirically derived definition of a clinically significant improvement. The receiver operating characteristics that differentiate patients with ADHD from community controls with the optimal area under the curve is a mean score of 0.65 (Thompson et al. 2017). Since this represents a value that places the patient in a domain of functional impairment no different from the population without ADHD, it is a reasonable and empirically derived definition of functional remission. The objective of this study is to determine the extent to which children and adolescents who meet the conventional definitions for symptom improvement and remission also meet empirical criteria for functional improvement and remission. Previous clinical trials have demonstrated that the WFIRS-P is sensitive to change in functional impairment (Banaschewski et al. 2013, 2014; Stein et al. 2015; Wilens et al. 2015; Nagy et al. 2016) and sensitive to change as measured against change in ADHD symptoms (Gajria et al. 2015).

The ADHD-RS-IV is an 18-item scale that rates each of the symptoms of ADHD as outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* (DSM-

IV-TR™) (DuPaul et al. 1998). Response to an ADHD treatment has been defined as an improvement in the ADHD-RS-IV of $\geq 30\%$, with remission defined as no longer meeting the ADHD diagnostic criteria (ADHD-RS-IV score ≤ 18) (Steele et al. 2006).

Definitions

For these analyses, the following definitions were applied: (1) symptom improvement was defined as a $\geq 30\%$ decrease (improvement) in ADHD-RS-IV total score; (2) symptom remission was defined as an ADHD-RS-IV total score ≤ 18 ; (3) functional improvement was defined as a decrease in WFIRS-P total score ≥ 0.25 (MID); and (4) functional remission was defined as a WFIRS-P total score ≤ 0.65 . It should be noted that Mattingly et al. (2017) previously demonstrated that a 30% decrease in symptoms (measured by ADHD-RS-IV total) and a CGI-I score of either much or very much improved were comparable definitions of improvement. Similarly, in the same study, it was found that a 50% decrease in symptoms or a mean total score on the ADHD-RS-IV of ≤ 18 was also a comparable definition of symptom remission.

Statistical analysis

Exact confidence intervals for proportions were used. Effect size for reduction in WFIRS-P total score was defined as the mean reduction divided by the SD at baseline. For studies with one-group, pre-post designs, the pre-group mean is usually subtracted from the post-group mean and divided by the SD at pre. (Durlak 2009). A two-sample *t*-test was used to compare treatment naive with nontreatment naive and to compare children with adolescents.

Results

A total of 221 children and adolescents entered and 200 completed the open-label phase. The population was mostly white, male, and had a mean (SD) age of 10.8 (3.0) years and mean (SD) weight of 45.0 (19.4) kg. The most prevalent ADHD presentation was combined (134/221, or 61%), with predominantly inattentive being most of the remaining children and adolescents (72/221, or 33%).

At baseline, mean ADHD-RS-IV total scores for treatment naive ($n = 148$) were similar to those for previously treated ($n = 73$; 36.0 vs. 36.4; $p = 0.77$); mean WFIRS-P total score indicated more functional impairment for treatment naive (0.82 vs. 0.70, $p = 0.02$; Table 1). The domains and subdomains with significant differences were Learning and School (1.18 vs. 0.84, $p < 0.001$), Learning (1.94 vs. 1.31, $p < 0.001$), and Life Skills (1.03 vs. 0.87, $p = 0.02$). WFIRS-P total and individual domain scores were similar for children and adolescents. Functional impairment was prevalent across WFIRS-P domains, with the greatest impairment in the Learning domain (Learning 1.73, Learning and School 1.07, Family 0.81, School Behavior 0.62, Life Skills 0.98, Self-concept 0.82, Social Activities 0.64, and Risky Activities 0.36; Fig. 1).

At the end of the open-label phase, statistically and clinically significant improvement in total and all functional domains was noted, with the largest improvement in the Learning domain (Fig. 2). Mean (SD) change from baseline in WFIRS-P score at the end of the open-label phase was as follows: total 0.27 (0.32), Family 0.27 (0.47), Learning and School 0.50 (0.56), Learning 0.74 (0.83), Behavior 0.44 (0.53), Life Skills 0.25 (0.47), Self-concept 0.41 (0.73), Social Activities 0.24 (0.43), and Risky Activities 0.18 (0.33). With the exception of Family, effect size for all domains was ≥ 0.50 , and Total, Learning/School, and Learning had effect sizes ≥ 0.75 .

TABLE 1. WEISS FUNCTIONAL IMPAIRMENT RATING SCALE-PARENT SCORE AT BASELINE BY ATTENTION-DEFICIT/HYPERACTIVITY DISORDER TREATMENT STATUS BEFORE STUDY ENTRY AND AGE GROUP

	Treatment naive (n=148 ^a)	Not treatment naive (n=73)	Child ^b (n=152 ^c)	Adolescent ^d (n=69)
WFIRS-P, mean (SD)				
Total*	0.82 (0.33)	0.70 (0.37)	0.78 (0.35)	0.79 (0.35)
Family	0.83 (0.60)	0.78 (0.60)	0.83 (0.61)	0.77 (0.59)
Learning and School	1.18 (0.60)	0.84 (0.60)	1.05 (0.58)	1.13 (0.69)
Learning	1.94 (0.84)	1.31 (0.89)	1.69 (0.89)	1.82 (0.93)
Behavior	0.66 (0.63)	0.53 (0.58)	0.59 (0.56)	0.66 (0.73)
Life Skills	1.03 (0.44)	0.87 (0.46)	0.94 (0.46)	1.05 (0.43)
Child's Self-concept	0.85 (0.70)	0.77 (0.77)	0.82 (0.73)	0.84 (0.71)
Social Activities	0.64 (0.46)	0.63 (0.49)	0.68 (0.49)	0.56 (0.41)
Risky Activities	0.36 (0.34)	0.34 (0.31)	0.36 (0.34)	0.35 (0.31)

^aN=147 (Family, Child's Self-concept, and Risky Activities), N=146 (Behavior).

^bAge 6–12 years inclusive.

^cN=151 (Family, Child's Self-concept, and Risky Activities), N=150 (Behavior).

^dThirteen to 18 years inclusive.

*p=0.02 treatment naive versus not treatment naive.

SD, standard deviation; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent.

Overall, at open-label end, 94% (188/200) of patients had symptom improvement ($\geq 30\%$ ADHD-RS-IV total score improvement) and 56% (112/200) had functional improvement (≥ 0.25 decrease in WFIRS-P total score). Of those with symptom improvement, only 57% (108/188) had functional improvement (Fig. 3) and 43% (80/188) did not have functional improvement. With 95% assurance, $\geq 35\%$ of patients with symptom improvement will not have functional improvement (95% confidence interval, 0.35–0.50). By contrast, of the 112 patients with functional improvement, only 4% did not have symptom improvement.

At open-label end, 75% (150/200) of children and adolescents were in symptom remission as defined by ADHD-RS-IV total score ≤ 18 . This was similar to 74% (147/200) with functional remission, defined as WFIRS-P total score ≤ 0.65 . Of the 150 children and

adolescents with symptom remission at the end of the open-label phase, 19% (29/150) were not in functional remission (WFIRS-P total score > 0.65 ; Fig. 4). Of the 147 with functional remission, 18% (26/147) did not have symptom remission.

Discussion

Treatment with MPH-MLR in children and adolescents who were functionally impaired resulted in significant improvements in WFIRS-P total score and all domains. The population of children and adolescents in this study had the most impairment in the Learning domain and experienced the greatest improvement in this area.

In our study, symptomatic improvement was noted in almost all children and adolescents and symptomatic remission was noted in a

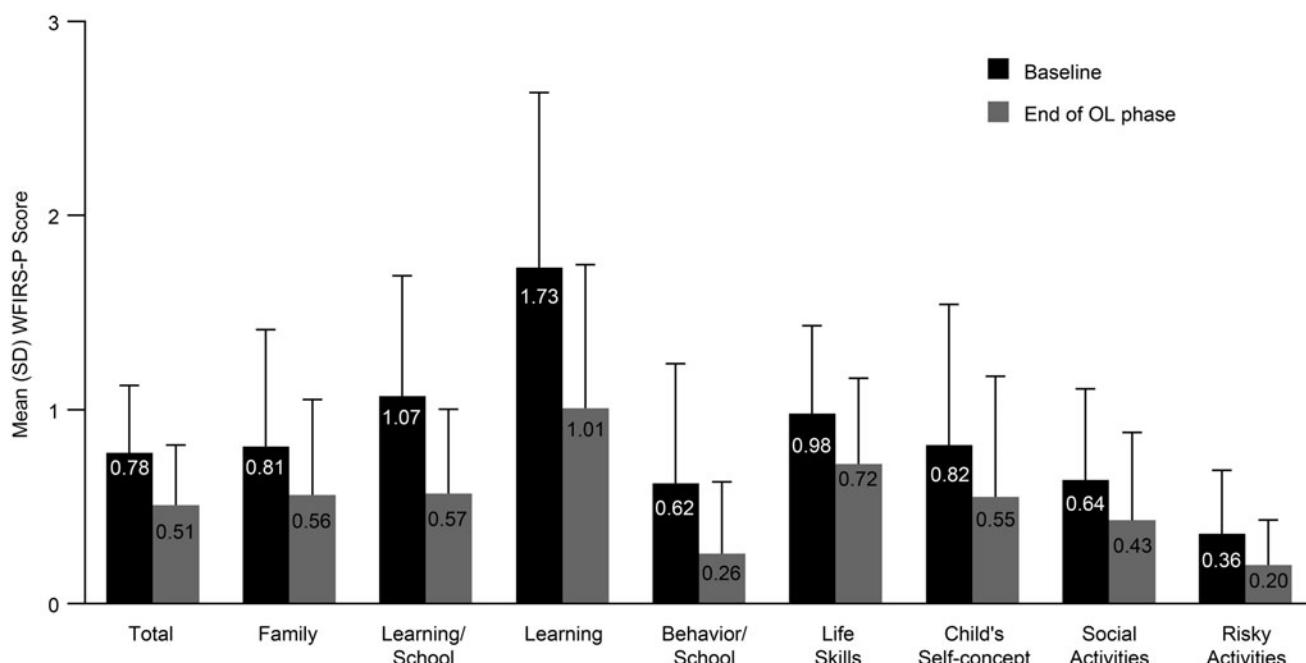


FIG. 1. WFIRS-P scores at baseline and end of the OL phase. OL, open-label; SD, standard deviation; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent.

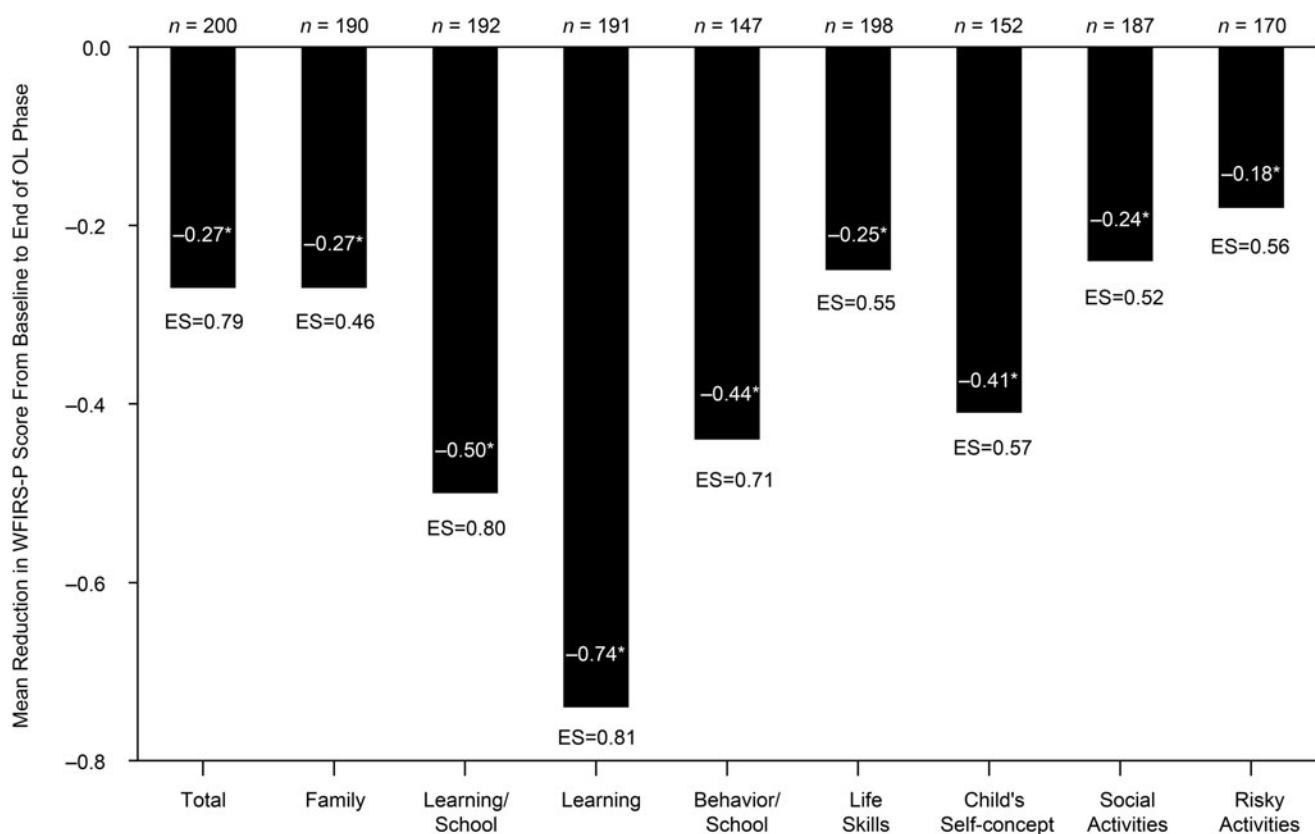


FIG. 2. Mean reduction in WFIRS-P score from baseline to end of the OL phase. ES, effect size (defined as mean reduction divided by standard deviation at baseline). * $p < 0.001$.

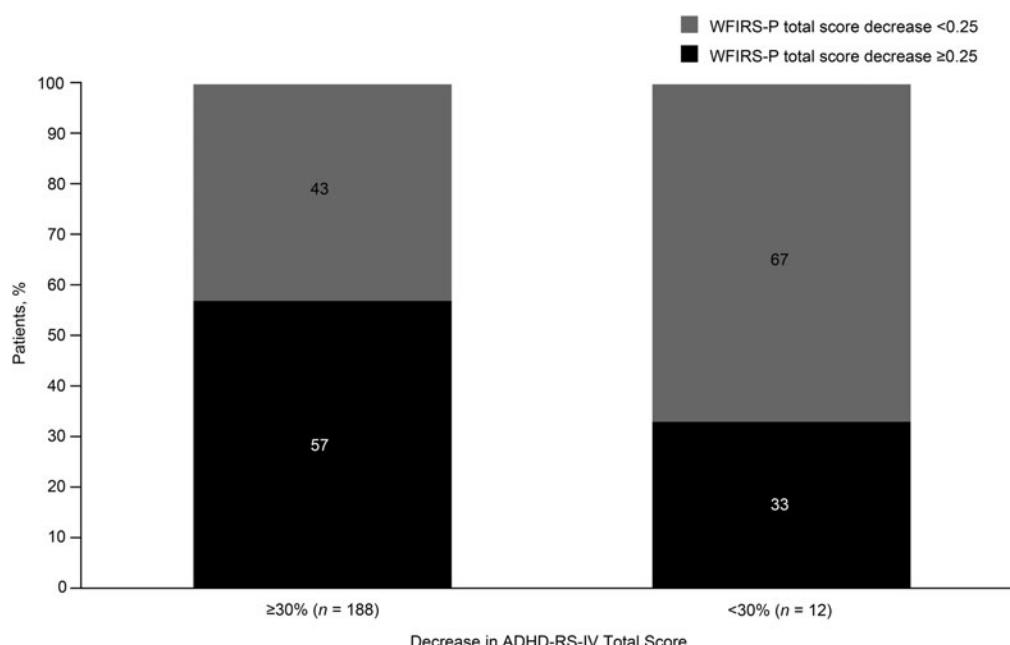


FIG. 3. Proportion of children and adolescents with functional improvement by symptom improvement* at end of the open-label phase. *Symptom improvement defined as ≥30% improvement in ADHD-RS-IV total score from baseline to end of the open-label phase; functional improvement defined as ≥0.25 improvement in WFIRS-P total score from baseline to end of the open-label phase ($n = 200$ at end of the open-label phase). ADHD-RS-IV, Attention-Deficit/Hyperactivity Disorder Rating Scale, Fourth Edition.

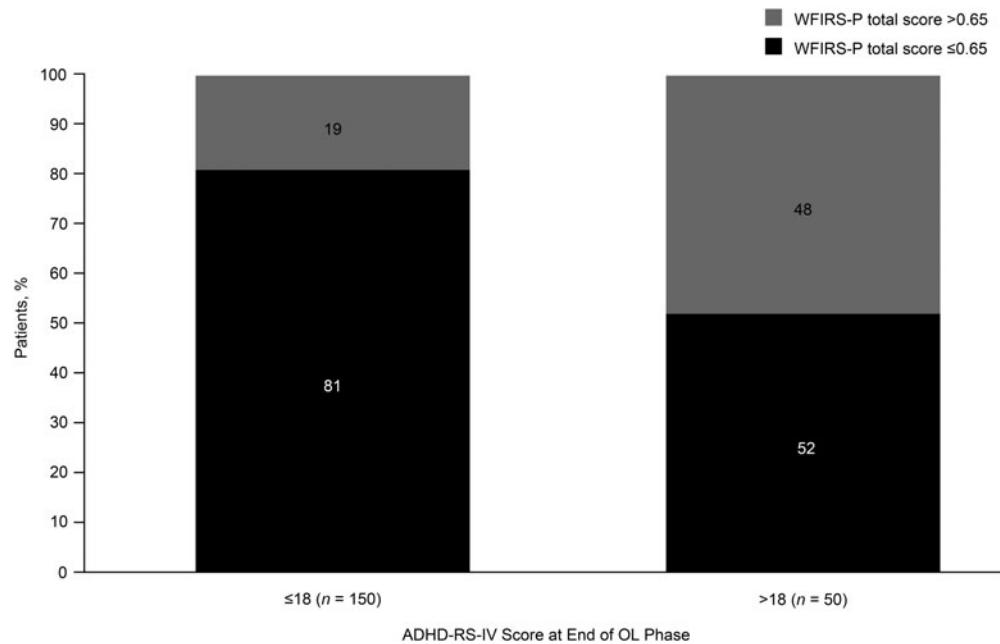


FIG. 4. Proportion of children and adolescents with functional remission* by symptom remission at end of the OL phase. *Remission defined as ADHD-RS-IV total score ≤ 18 (symptom) or WFIRS-P total score ≤ 0.65 (functional).

majority of the study population. Only 57% of the population studied, who had symptom improvement also showed functional improvement, while 96% of those who had functional improvement also had symptom improvement. This lack of complete alignment between symptom improvement/remission and functional improvement/remission cannot be explained solely by the concept that functional impairment is driven by factors other than ADHD, because almost all of those who reached the defined measure of functional remission also had symptom remission. Alignment between these measures would be expected and consistent with the definition of functional impairment used in the WFIRS-P, describing difficulties in functioning secondary to the symptoms of the disorder. Even for patients in symptomatic remission, however, assessment of functional impairment remains clinically significant.

It should be noted that using the WFIRS-P MID definition of 0.25 for improvement and the receiver operating characteristics definition of 0.65 as the cutoff that differentiates ADHD from normal controls means that remission is not necessarily a more robust indicator of response than improvement. The population had enough children with mild impairment that 74% met the criteria for remission based on endpoint score, while only 56% met the criteria for improvement based on the degree of change. Further research is necessary to look at how these empirically based definitions of improvement compare to definitions of functional improvement and response similar to those used for symptoms based just on change, that is, a 30% versus 50% change in score and improvement versus remission outcomes in samples that have more severe functional impairment.

Medication treatment of children and adolescents with ADHD has resulted in improvements in functioning. In a placebo-controlled comparison study of the dose effects of extended-release dextroamphetamine and extended-release mixed amphetamine salts, the WFIRS-P was used to evaluate functional response to 8 weeks of treatment in 56 children and adolescents with ADHD (Stein et al.

2011). Statistically significant dose effects were noted in WFIRS-P total ($p=0.008$) and the Family ($p=0.001$), Learning ($p=0.002$), Social Activities ($p=0.018$), and Risk-Taking ($p=0.050$) subscales that were similar for the two study drugs, with no impact of treatment noted for the Living Skills or Self-Esteem subscales. Dose-related symptom improvements also were noted in this study using both the ADHD-RS-IV and the CGI-I.

In this study, gains were seen in all domains, with the most robust improvement seen in School Learning, which was also the domain most impaired at baseline in this particular sample. These results are consistent with other trials. The domain of Risky Activities has somewhat lower baseline scores than other domains, and taps rare, but salient events that may have high clinical impact even if there are floor effects or lower values than the absolute scores. Some authors (Dose et al. 2016) have assumed that the domain of Risky Activities is not relevant to a younger population. However, our data demonstrate not only that the domain is relevant, but also that improvement in this domain may have significant impact on the high-risk outcomes of children and adolescents with ADHD.

The WFIRS-P was used to evaluate functional impairment in a 7-week, randomized, double-blind, placebo-controlled evaluation of lisdexamfetamine or OROS methylphenidate as reference in children and adolescents with ADHD (Banaschewski et al. 2013). For lisdexamfetamine-treated patients, there was evidence of functional improvement, evidenced by statistically significant changes in WFIRS-P by week 4 (Total, Learning and School, Social Activities, and Risky Activities), and by week 7 in the remaining domains. OROS methylphenidate-treated patients followed a similar pattern. In the primary evaluation of these data, significant improvements in ADHD-RS-IV scores were noted in both study treatment groups (Coghill et al. 2013).

Comparison of stimulant versus nonstimulant outcomes in functional impairment suggests a more robust improvement in functional impairment with stimulants. In that same study, lisdexamfetamine

showed more robust improvement than OROS methylphenidate and atomoxetine (Coghill et al. 2017). This may reflect the increased parent perception of difference in outcome based on clear demarcations between periods on and off medication. It should be noted that in this study of a long-acting methylphenidate product, robust improvement was shown in all domains in open-label follow-up, consistent with the outcomes of lisdexamfetamine. This study also confirms the hypothesis laid out by Coghill et al. (2017) that neither symptom evaluation nor functional evaluation alone are sufficient to allow the clinician to make appropriate decisions about whether and what further intervention is required.

In summary, our study replicates previous studies in demonstrating that treatment with medication leads to improvement in both symptoms and functional impairment. Our findings are unique in that we have been able to show that a significant fraction of children with symptom improvement and remission with stimulant medication may continue to show functional impairment, warranting further clinical intervention.

Limitations

This article presents the results of a *post hoc* analysis. Only a very small percentage of the population was predominantly hyperactive ADHD subtype and results may or may not be applicable to this subtype. Although we have used reasonable psychometric and empirically derived overall scores of functional improvement and functional remission, it is possible for children to show overall improvement, but still experience impairment in a particular domain, or conversely to show dramatic and clinically significant improvement in a domain that is not sufficient to meet the cutoff of 0.25 for the scale as a whole. Similarly, the definition we used for functional remission is based on the cutoff score that differentiates ADHD from normal controls, but cannot be taken to mean that the child has no residual impairment. The study results reported are open label, and therefore the extent to which functional improvement was driven by treatment as opposed to time is unclear. However, the results appear to be largely consistent with the expected gains in functional impairment seen with change in symptoms, and there is little to suggest that children with ADHD show systematic gains in functioning with time alone. The greatest gains seen were in domains of School and Learning, but this was based on parent report since no teacher evaluations were included. Since there is modest correlation between teacher and parent report, and teachers typically report greater change at school than parents, these results may be an underestimate of the response seen in the school setting. In addition, because this is an open-label single-group study, the effect sizes should be interpreted with caution.

Conclusions

Treatment with MPH-MLR resulted in improvement on the total score and all domain scores of the WFIRS-P as well as functional remission in 74% of children and adolescents. Approximately half of the children and adolescents who achieved symptom improvement (30% change in ADHD-RS-IV) also achieved functional improvement, and symptom remission (mean score ≤ 18) was associated with an achievement of functional remission in >80% of children and adolescents. This suggests that targeting remission as a goal of symptom response has a direct impact on real-life gains in function. These results highlight the need to assess improvement and remission of both symptoms and functioning in clinical studies. Additional therapeutic modalities may be needed in children and adolescents with persistent functional impairment

despite symptom normalization, and additional therapeutic interventions may be required.

Clinical Significance

Both symptom improvement and functional improvement as well as symptom and functional remission were observed in children treated with MPH-MLR. Seventy-five percent of children achieved symptom remission and 74% achieved functional remission. Functional remission was achieved in >80% of those with symptom remission. Targeting remission as a goal of symptom response appears to have a direct impact on real-life gains in function and suggests that clinical studies need to assess improvement and remission of both symptoms and functioning.

Acknowledgments

The authors would like to acknowledge the contributions of all study participants, their guardians, and investigators. Medical writing support was provided by Linda Wagner, PharmD, from Excel Scientific Solutions, and funded by Rhodes Pharmaceuticals L.P.

Authors' Contributions

Data for this article were analyzed by E.N.; data interpretation was provided by all authors. M.W. wrote the first draft and all authors provided input into revising the article and approved the final version for publication.

Disclosures

Dr. Weiss is a consultant for and/or speakers' bureau member for Eli Lilly, Janssen, Purdue, Rhodes Pharmaceuticals L.P., and Shire, and has received research support from Purdue.

Dr. Childress receives research support from Alcobra, Arbor, Forest, Ironshore, Lilly, Lundbeck, Medgenics, Neos, Neurovance, NextWave, Noven, Otsuka, Pearson, Pfizer, Purdue, Rhodes Pharmaceuticals L.P., Shire, Sunovion, Theravance, and Tris; is a consultant for and has received honoraria from Ironshore, Neos, Pfizer, Rhodes Pharmaceuticals L.P., and Shire; has received travel support from Ironshore, NextWave, Pfizer, and Shire; has received writing assistance on projects from Arbor, Ironshore, Neos, NextWave, Pfizer, Rhodes Pharmaceuticals L.P., and Shire; has received payment for lectures from Arbor, Pfizer, and Shire; and is a member of the advisory board for Arbor, Ironshore, Neos, Neurovance, NextWave, Noven, Pfizer, and Rhodes Pharmaceuticals L.P.

Dr. Mattingly is a speaker for Forest, Lundbeck, Merck, Otsuka, Shire, Sunovion, and Takeda, and is a consultant or performed research for Alcobra, Alkermes, Forest, Forum, Janssen, Lundbeck, Merck, Novartis, Niven, Otsuka, Pfizer, Purdue, Reckitt Benckiser, Rhodes Pharmaceuticals L.P., Shire, Sunovion, Takeda, and Vanda.

Dr. Nordbrock is a consultant for Rhodes Pharmaceuticals L.P.

Dr. Kupper and Dr. Adjei are employees of Rhodes Pharmaceuticals L.P.

References

- Aptensio XR® capsules [package insert]. Coventry (Rhode Island), Rhodes Pharmaceuticals L.P. Revised May 2015.
- Adjei A, Teuscher NS, Kupper RJ, Chang WW, Greenhill L, Newcorn JH, Connor DF, Wigal S: Single-dose pharmacokinetics of methylphenidate extended-release multiple layer beads administered as intact capsule or sprinkles versus methylphenidate immediate-release

- tablets (Ritalin[®]) in healthy adult volunteers. *J Child Adolesc Psychopharmacol* 24:570–578, 2014.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Association, 2013.
- Axelrod BN: Validity of the Wechsler Abbreviated Scale of Intelligence and other very short forms of estimating intellectual functioning. *Assessment* 9:17–23, 2002.
- Banaschewski T, Johnson M, Lecendreux M, Zuddas A, Adeyi B, Hodgkins P, Squires LA, Coghill DR: Health-related quality of life and functional outcomes from a randomized-withdrawal study of long-term lisdexamfetamine dimesylate treatment in children and adolescents with attention-deficit/hyperactivity disorder. *CNS Drugs* 28:1191–1203, 2014.
- Banaschewski T, Soutullo C, Lecendreux M, Johnson M, Zuddas A, Hodgkins P, Adeyi B, Squires LA, Coghill D: Health-related quality of life and functional outcomes from a randomized, controlled study of lisdexamfetamine dimesylate in children and adolescents with attention deficit hyperactivity disorder. *CNS Drugs* 27:829–840, 2013.
- Buitelaar J, Medori R: Treating attention-deficit/hyperactivity disorder beyond symptom control alone in children and adolescents: A review of the potential benefits of long-acting stimulants. *Eur Child Adolesc Psychiatry* 19:325–340, 2010.
- Canadian ADHD Resource Alliance: CADDRA ADHD Assessment Toolkit (CATT) Forms. 2011. Available at: www.caddra.ca/cms4/pdfs/caddraGuidelines2011_Toolkit.pdf Accessed October 27, 2014.
- Canadian ADHD Resource Alliance: Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P). 2000. Available at: www.caddra.ca/cms4/pdfs/caddraGuidelines2011WFIRS_P.pdf Accessed June 22, 2016.
- Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, Anderson C, Civil R, Higgins N, Lyne A, Squires L: European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. *Eur Neuropsychopharmacol* 23:1208–1218, 2013.
- Coghill DR, Joseph A, Sikirica V, Kosinski M, Bliss C, Huss M: Correlations between clinical trial outcomes based on symptoms, functional impairments, and quality of life in children and adolescents with ADHD. *J Atten Disord* 2017. [Epub ahead of print]; DOI: 10.1177/1087054717723984.
- Dose C, Hautmann C, Doepfner M: Functional impairment in children with externalizing behavior disorders: Psychometric properties of the Weiss Functional Impairment Rating Scale-Parent Report in a German clinical sample. *J Atten Disord* 2016. [Epub ahead of print]; DOI: 10.1177/1087054716661234.
- DuPaul GJ, Power TJ, Anastopoulos AD, Reid R: ADHD Rating Scale-IV: Checklist, Norms, and Clinical Interpretation. New York, Guilford Press, 1998.
- Durlak JA: How to select, calculate, and interpret effect sizes. *J Pediatr Psychol* 34:917–928, 2009.
- Epstein JN, Weiss MD: Assessing treatment outcomes in attention-deficit/hyperactivity disorder: A narrative review. *Prim Care Companion CNS Disord* 14: 2012. DOI: 10.4088/PCC.11r01336.
- Gajria K, Kosinski M, Sikirica V, Huss M, Livote E, Reilly K, Dittmann RW, Erder MH: Psychometric validation of the Weiss Functional Impairment Rating Scale-Parent Report Form in children and adolescents with attention-deficit/hyperactivity disorder. *Health Qual Life Outcomes* 13:184, 2015.
- Guy W: ECDEU Assessment Manual for Psychopharmacology—Revised (DHEW Publ No. ADM 76-338). Rockville, MD, U.S. Department of Health, Education, and Welfare, Public Health Services, Alcohol, Drug Abuse, and Mental Health Administration, 1976.
- NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, 1976.
- Hadianfarid H, Kiani B, Weiss MD: Psychometric properties of the Persian version of the Weiss Functional Impairment Rating Scale-self-report form in Iranian adolescents. *J Atten Disord* 2017. [Epub ahead of print]; DOI: 10.1177/1087054717738084.
- Hodgkins P, Lloyd A, Erder MH, Setyawan J, Weiss MD, Sasane R, Nafees B: Estimating minimal important differences for several scales assessing function and quality of life in patients with attention-deficit/hyperactivity disorder. *CNS Spectr* 22:31–40, 2017.
- Jacobson NS, Truax P: Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 59:12–19, 1991.
- Mattingly G, Childress A, Nordbrock E, Adjei A, Kupper RJ, Weiss M: Clinical response and symptomatic remission with Aptensio XR[®] (methylphenidate extended-release capsules) in children and adolescents with ADHD. American Professional Society ADHD and Related Disorders (APSARD) Annual Meeting, Washington, DC, 2017.
- Molina BS, Hinshaw SP, Swanson JM, Arnold LE, Vitiello B, Jensen PS, Epstein JN, Hoza B, Hechtman L, Abikoff HB, Elliott GR, Greenhill LL, Newcorn JH, Wells KC, Wigal T, Gibbons RD, Hur K, Houck PR; MTA Cooperative Group: The MTA at 8 years: Prospective follow-up of children treated for combined-type ADHD in a multisite study. *J Am Acad Child Adolesc Psychiatry* 48:484–500, 2009.
- Nagy P, Häge A, Coghill DR, Caballero B, Adeyi B, Anderson CS, Sikirica V, Cardo E: Functional outcomes from a head-to-head, randomized, double-blind trial of lisdexamfetamine dimesylate and atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder and an inadequate response to methylphenidate. *Eur Child Adolesc Psychiatry* 25:141–149, 2016.
- Punyapas S, Pornnoppadol C, Boon-ysadhi V, Likhitkiatikhachorn P: Reliability and validity of Weiss Functional Impairment Rating Scale (WFIRS)-Thai version in children and adolescents with attention deficit hyperactivity disorder. *J Psychiatric Assoc Thai* 60: 111–126, 2015.
- Qian Y, Du Q, Qu S, Wang Y: Reliability and validity of the Chinese version of Weiss Functional Impairment Scale-Parent Form for school age children. *Chin Ment Health J* 25:767–771, 2011.
- Quitkin FM, McGrath PJ, Stewart JW, Deliyannides D, Taylor BP, Davies CA, Klein DF: Remission rates with 3 consecutive antidepressant trials: Effectiveness for depressed outpatients. *J Clin Psychiatry* 66:670–676, 2005.
- Steele M, Jensen PS, Quinn DM: Remission versus response as the goal of therapy in ADHD: A new standard for the field? *Clin Ther* 28:1892–1908, 2006.
- Stein MA, Sikirica V, Weiss MD, Robertson B, Lyne A, Newcorn JH: Does guanfacine extended release impact functional impairment in children with attention-deficit/hyperactivity disorder? Results from a randomized controlled trial. *CNS Drugs* 29:953–962, 2015.
- Stein MA, Waldman ID, Charney E, Aryal S, Sable C, Gruber R, Newcorn JH: Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. *J Child Adolesc Psychopharmacol* 21:581–588, 2011.
- Swanson JM, Kraemer HC, Hinshaw SP, Arnold LE, Conners CK, Abikoff HB, Clevenger W, Davies M, Elliott GR, Greenhill LL, Hechtman L, Hoza B, Jensen PS, March JS, Newcorn JH, Owens EB, Pelham WE, Schiller E, Severe JB, Simpson S, Vitiello B, Wells K, Wigal T, Wu M: Clinical relevance of the primary findings of the MTA: Success rates based on severity of ADHD and ODD symptoms at the end of treatment. *J Am Acad Child Adolesc Psychiatry* 40:168–179, 2001.

- Tarakçioğlu MC, Memik NÇ, Olgun NN, Aydemir Ö, Weiss MD: Turkish validity and reliability study of the Weiss Functional Impairment Rating Scale-Parent Report. *Atten Defic Hyperact Disord* 7:129–139, 2015.
- Thompson T, Lloyd A, Joseph A, Weiss M: The Weiss Functional Impairment Rating Scale-Parent Form for assessing ADHD: Evaluating diagnostic accuracy and determining optimal thresholds using ROC analysis. *Qual Life Res* 26:1879–1885, 2017.
- Weiss MD, Brooks BL, Iverson GL, Lee B, Dickson R, Gibbins C, Wasdell M: Reliability and validity of the Weiss Functional Impairment Rating Scale. American Academy of Child and Adolescent Psychiatry 64th Annual Meeting, Washington, DC, 2007.
- Weiss MD, Wasdell MB, Bomben MM, Caney SV: Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P): A new measure of impairment associated with ADHD. 158th Annual Meeting of the American Psychiatric Association, Atlanta, GA, 2005.
- Wigal SB, Greenhill LL, Nordbrock E, Connor DF, Kollins SH, Adjei A, Childress A, Stehli A, Kupper RJ: A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 24:562–569, 2014.
- Wigal SB, Nordbrock E, Adjei AL, Childress A, Kupper RJ, Greenhill L: Efficacy of methylphenidate hydrochloride extended-release capsules (Aptensio XRTM) in children and adolescents with attention-deficit/hyperactivity disorder: A phase III, randomized, double-blind study. *CNS Drugs* 29:331–340, 2015.
- Wilens TE, Robertson B, Sikirica V, Harper L, Young JL, Bloomfield R, Lyne A, Rynkowski G, Cutler AJ: A randomized, placebo-controlled trial of guanfacine extended release in adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 54:916–925.e2, 2015.

Address correspondence to:
Margaret Weiss, MD, PhD, FRCP(C)

*Child and Adolescent Psychiatry
Child Study Center
11 Children's Way
Little Rock, AR 72202*

E-mail: mdweiss@uams.edu